

Dietary Polycyclic Aromatic Hydrocarbon (PAH) Consumption and Risk of Adverse Birth Outcomes: A Systematic Review and Meta-Analysis

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BACKGROUND: There is suggestive epidemiological evidence that maternal dietary polycyclic aromatic hydrocarbons (PAH) may increase the risk of adverse birth outcomes. We sought to summarize the available evidence on the effect of dietary PAH exposure on birth outcomes.

METHODS: PubMed and Scopus databases were systematically searched from inception up to November 2022. Studies were included if they were original articles, were conducted in a human population, assessed dietary PAH consumption, and investigated the relationship between dietary PAH consumption and any adverse birth outcomes. Risk of bias in the included studies was assessed qualitatively and quantitatively. A random effects model was used to compute summary effect estimates in the meta-analysis.

RESULTS: Six observational studies (five prospective cohort studies, and one prevalence case–control study) were included. The included studies assessed dietary PAH exposure using dietary questionnaires. Information on the outcomes of interest was obtained from medical records. Three of the included studies were rated as good quality with the remaining three studies rated as fair quality. One study was considered as having low risk of bias for selection, information and confounding bias. Dietary PAH consumption was associated with 5.65 g [95% confidence interval (CI): –16.36, 5.06] and 0.04 cm (95% CI: –0.08, 0.01) reductions in birth weight and birth length, respectively, and an increase in head circumference [effect size (ES) = 0.001; 95% CI: –0.003, 0.005]. The CI of all the summary effect estimates, however, included the null value. In the sensitivity analysis that included only studies that assessed dietary PAH exposure as the primary exposure of interest, dietary PAH consumption was associated with much higher reductions in birth weight (ES = –14.61; 95% CI: –21.07, –8.15) and birth length (ES = –0.06; 95% CI: –0.1, –0.03). High statistical heterogeneity was observed in the birth weight and birth length analysis and in the head circumference sensitivity analysis.

DISCUSSION: The body of epidemiological evidence suggests that maternal dietary PAH exposure is associated with reduced fetal growth, measured as birth weight and length. There was considerable heterogeneity in the measurement of PAH exposure among the included studies. Also, nonstandardized and validated dietary questionnaires were employed by a majority of the included studies with potential exposure misclassification. These issues are likely to impact the summary effect estimates computed and underscores the need for high-quality epidemiological studies with improved exposure assessment and adequate confounding control to strengthen the evidence base. <https://doi.org/10.1289/EHP12922>

Background

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous pollutants formed from the incomplete combustion of biomass and fossil fuels, emissions from vehicle exhaust, power generation, tobacco smoke, and food products.^{1–3} Several hundred different PAHs species exist, with 15 of them including benz[a]anthracene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and dibenzo[a,e]pyrene, reported by a number of international scientific bodies, including the European Commission, the International Program on Chemical Safety, the Scientific Committee on Food, and the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives, to pose harmful effects on human health.⁴

Diet is a common and important route of nonoccupational exposure to PAHs.^{7,8} A number of epidemiological studies have reported high levels of PAHs in many food groups, including meat and meat products, cereals, and fats and oils.^{5,6} Dietary exposure to

PAHs can result from food processing methods. Consumption of processed or cooked foods that have been subjected to high-temperature methods, such as grilling, smoking, roasting, and frying, has been reported as the main source of dietary PAH exposure.^{7,8} For instance, the average PAH levels in uncooked foods are expected to be within the range of 0.01–1 µg/kg. However, levels in barbecued meat and smoked fish have been reported to be as high as 130 µg/kg and 200 µg/kg, respectively.⁹ Direct fire drying, where combustion products come into contact with oil seeds or oil may also contaminate vegetable oils with PAH.¹⁰ The deposition of airborne PAHs on food products during processing and storage also contributes to dietary exposure to PAH.⁹ In spite of diet being identified as the common route of PAH exposure, several studies have also found inhalation of airborne PAH as well as tobacco smoke to be an equally important routes of exposure.^{1,11,12}

Exposure to PAHs is a major public health concern due to its adverse health effects.^{13,14} PAHs have been identified as a well-known reproductive toxicant that affects both the mother and the developing fetus.¹⁵ PAHs have the potential to bioaccumulate in pregnant women and reach the fetus via transplacental transfer with adverse consequences for fetal health and development.^{15,16} A meta-analysis conducted by Yang et al.¹⁷ found no association between maternal airborne PAH exposure and birth weight [Odds ratio (OR) = 0.97; 95% CI: 0.93, 1.01]. Reviews on the impact of industrial¹⁸ and smoking-related¹⁹ PAH exposure, however, suggest that PAH exposure from these environmental sources may have adverse effects on pregnancy (e.g., preeclampsia) and birth outcomes (reduced head circumference and small for gestational age).

There is a growing number of epidemiological studies investigating the association of dietary PAH exposure with the risk of adverse birth outcomes including low birth weight (LBW), preterm birth (PTB) and small for gestational age (SGA), with these studies

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reporting conflicting findings. To date, based on a systematic literature search, no study has summarized the body of evidence on the relationship. We therefore conducted a systematic review and meta-analysis of the epidemiological studies on the relationship to assess the quality and strength of the available evidence, to identify the gaps in knowledge, and to propose future research directions. The findings of the study will help inform dietary guidance to pregnant women to improve birth outcomes.

Methods

We registered the study protocol with PROSPERO (Registration number: CRD42021256200). We report the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁰

Information Sources and Search Strategy

PubMed and Scopus databases were searched from their inception to the end of November 2022 without the imposition of any language restrictions. The search statement applied in the databases was [(“Polycyclic aromatic hydrocarbons” OR PAH) AND (still-birth OR “fetal death” OR “fetal mortality” OR “perinatal death” OR “perinatal mortality” OR “spontaneous abortion” OR miscarriage OR “preterm birth” OR PTB OR “preterm delivery” OR “pre-mature birth” OR “birth weight” OR “low birth weight” OR LBW OR “gestational age” OR “small for gestational age” OR SGA OR “intrauterine growth retardation” OR IUGR OR “pregnancy outcome*” OR “birth outcome*” OR “perinatal outcome*” OR “fetal growth”)]. The articles were initially screened for eligibility based on the title and abstract by two independent investigators (C.S. and A.K.A.).

Eligibility Criteria and Study Selection

Articles were considered for inclusion if they satisfied the following: *a*) original articles of any epidemiological design *b*) conducted in a human population, *c*) assessed dietary PAH consumption using any dietary assessment method, and *d*) provided empirical evidence on the relationship between dietary PAH consumption and risk of any of the listed outcomes in the search statement.

We retrieved selected articles in full and further assessed them for eligibility. For studies to qualify for inclusion, they must have either provided effect estimates for the relationship between dietary PAH consumption and the outcomes of interest or reported the proportion of cases of any of the outcomes of interest among mothers who did or did not consume PAH-rich foods. The reference lists of all included studies and the previous related reviews were also reviewed to identify additional eligible studies. The characteristics of the studies excluded after reviewing the full articles for eligibility are provided in Table S1.

Data Extraction and Quality Assessment of Included Studies

The two investigators independently extracted data from eligible studies into a data extraction form. During synthesis of the data extracted, any disagreements were resolved through discussion until a consensus was reached. We assessed methodological quality of the included studies using two qualitative methods: *a*) National Institutes of Health (NIH) Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case–Control study (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>)²¹ and *b*) risk of bias assessment provided by Dekkers et al.²² Following recommendations in Dekkers et al.,²² we assessed risk of confounding, selection bias, and information bias in the included studies on three levels: low, moderate, and high. The NIH Study Quality Assessment Tool contains a set of questions for evaluating the

quality of epidemiological studies of any design on the basis of their design characteristics and applicability, including clarity of research questions, specification of study population, participation rate, sample representativeness, temporality, measurement of exposures, outcomes and covariates, blinding of outcome assessors, and attrition rate.

The risk of bias assessment was based on an objective evaluation of selection, information, and confounding bias in the included studies made possible by information provided in the reports or its absence in the report.

For selection bias, we evaluated *a*) sample representativeness, *b*) participation and response rate, *c*) missing data, *d*) attrition rate (for prospective studies), and *e*) data restrictions during the analysis. The low, moderate, and high ratings were based on studies ticking four or five boxes (low bias), three boxes (moderate bias), and two or fewer boxes (high bias).

For information bias, we evaluated the exposure and outcome assessment methods. Studies that used very robust exposure assessment methods [e.g., biomarkers or validated semiquantitative food frequency questionnaire (FFQ)] and with the outcomes measured in hospitals were rated as low bias. Studies that used dietary questionnaires other than FFQ but validated to assess exposure, and with the outcomes measured in hospitals, were rated as moderate bias. Studies that used nonvalidated dietary questionnaires to assess exposure, and with the outcome measured in hospitals, were rated as high bias.

For confounding bias, we searched for evidence of the studies controlling for potential confounders of the relationship in the multivariable analysis. Studies with adequate control of confounding were rated as low bias. Studies with inadequate control of confounding were rated as moderate bias. Studies with no control of confounding were rated as high bias.

For the NIH Study Quality Assessment (see Tables 3 and 4), we were guided by the set of questions provided for evaluating quality of epidemiological studies based on characteristics of the design. The questions included clarity of research questions, specification of study population, participation rate, sample representativeness, temporality, measurement of exposures, outcomes and covariates, blinding of outcome assessors, and attrition rate. Both assessments were independently conducted by two investigators (C.S. and A.K.A.), with a meeting after the independent assessments to agree on the ratings for each study.

Statistical Analyses

The random effects model, which accounts for both within- and between-study heterogeneity was used in computing the summary effect estimates. Studies providing multiple effect estimates were first combined using the fixed effects model and applying the single effect estimate in the overall meta-analysis. The Cochran Q (χ^2) test and the I^2 statistic was used to quantify heterogeneity, with a value of 50% deemed to indicate substantial heterogeneity. We visually inspected forest plots. The weights of the studies to the summary effect estimates computed were generated based on the inverse of the variance.²³ We conducted sensitivity analysis by limiting the analysis to studies that examined the dietary PAH exposure and birth outcomes relationship directly. We investigated publication bias by visually inspecting funnel plots for asymmetry and conducting the Begg’s and Egger’s tests. The trim and fill method was used to account for publication bias. Stata version 17.0 (Stata Corporation, Inc.) was used to conduct the analyses.

Results

A flowchart showing how the six studies were selected for inclusion in the study is depicted in Figure 1.

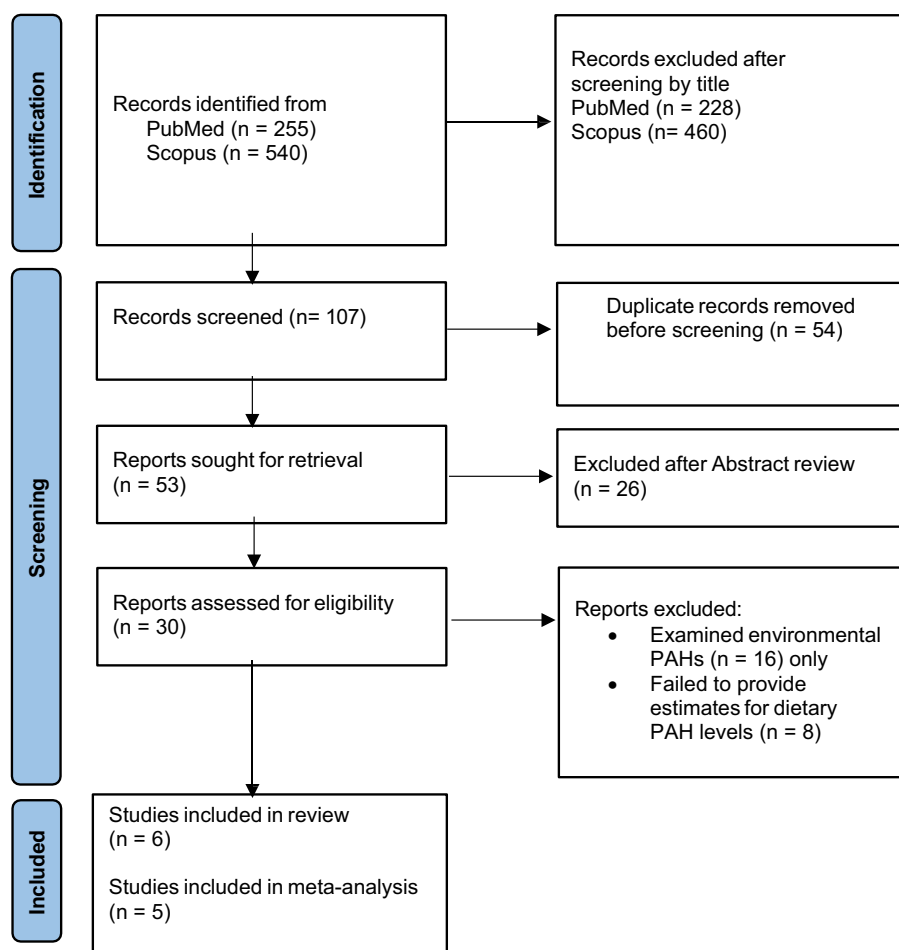


Figure 1. PRISMA diagram of the study selection process.

Characteristics of the Included Studies

The characteristics of the included studies are summarized in Table 1. Of the studies included, five were prospective cohort studies,^{24–28} and one was a prevalence case–control study.²⁹ Two of the included studies were conducted in China,^{27,29} with one each conducted in Norway,²⁴ Poland,²⁸ South Korea,²⁵ and the United States.²⁸

All the included studies assessed dietary consumption of PAH-rich foods using a dietary questionnaire, with two studies^{24,26} indicating using a food frequency questionnaire (FFQ). The FFQ was validated by the two studies, with Duarte-Salles et al.²⁴ validating the questionnaire among pregnant women and Lamichhane et al.²⁶ among an adult population. Both studies validated the FFQ for several nutrients and various food groups but not dietary PAH consumption. Of the studies using a questionnaire other than FFQ, one of the studies (Nie et al.²⁷) reported validating the dietary questionnaire but with no mention of the population in which the questionnaire was validated. The Lamichhane et al.²⁶ study computed food scores using the information collected in the FFQ and treated the data as a continuous variable in the analysis. Duarte-Salles et al.²⁴ on the other hand estimated daily dietary intake of benzo(a)pyrene using a food composition table and reported them in tertiles of intake. Jedrychowski et al.²⁵ and Wu et al.²⁹ assessed dietary PAH exposure as a binary outcome in the questionnaire by asking the study participants whether or not they consumed PAH-rich foods. The common foods assessed by the included studies were grilled, smoked, and roasted meat and fish.

Two of the included studies (Nie et al.²⁷ and Perera et al.²⁸) did not assess the dietary PAH exposure and birth outcomes relationship directly but indirectly through examination of the potential confounding role of dietary PAH exposure (treated as a binary variable) in the multivariable analysis. Nie et al.²⁷ investigated the association of maternal urinary 2-hydroxynaphthalene with birth outcomes in Taiyuan, China. Perera et al.²⁸ on the other hand assessed the effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population of New York, New York, in the United States.

Two of the included studies^{24,26} estimated gestational length using both ultrasound and last menstrual period (LMP) methods. Two studies^{28,29} used one method only to assess gestational age, with Perera et al.²⁸ using the LMP method and Wu et al.²⁹ the ultrasound method. One study (Perera et al.²⁹) investigated missed abortion, with the remaining five studies investigating one or more of the following birth anthropometric measures; birth weight,^{24–28} birth length,^{24–28} head circumference,^{25–28} and ponderal index and cephalization index.²⁷

Methodological Quality of Included Studies

The risk of bias assessment are summarized in Table 2. Evaluation of selection bias in the included studies was difficult, owing to the included studies failing to provide information on how sample size was determined and the sampling strategy adopted. Only the Duarte-Salles et al.²⁴ study provided information on the response rate. All the included studies provided information on the number of participants excluded from the analysis owing to missing

Table 1. Characteristics of included studies.

Author details	Study design, location and period	Population, sampling procedure, and follow-up	Exposure assessment	Outcome measurement	Covariates
Duarte-Salles et al. ²⁴	Prospective cohort study Norway 1998–2008	A total of 62,124 mothers who had baseline, dietary and maternal health information at the time of delivery were included; 15,704 mothers were excluded from the analysis for multiple reasons such as multiple pregnancies, preterm or post-term birth, maternal smoking during pregnancy, missing data, maternal energy intake, and withdrawal from the study.	Dietary consumption of 255 PAH [B(a)P]–rich foods was assessed using a semiquantitative FFQ during the first and second trimester of pregnancy (up to the fifth month). Intake of dietary supplements was also assessed. FFQ was validated among pregnant women for various nutrient intakes. A food composition table was used to estimate energy-adjusted dietary B(a)P intake in foods consumed. Assessed during 23–24 wk of the pregnancy (one time point). Treated as tertiles LOD: not reported Dietary consumption of PAH-rich foods (grilled, broiled, fried, or smoked meat) during each trimester was assessed using a detailed questionnaire. Assessed during first, second, and third trimester: Analysis focused on third trimester exposures Treated as a dichotomous variable	Birth weight and birth length Data obtained from medical records and measured by attending midwife Gestational age was estimated using LMP method and ultrasound data	Gestational age, sex of the child, age of the mother, parity, prepregnancy BMI, maternal weight gain, smoking during pregnancy, plausibility of energy intake and vitamin C intake
Jedrychowski et al. ²⁵	Prospective cohort study Krakow, Poland 01/2001 and 02/2004	A total of 432 pregnant women age ≥ 18 y who were nonsmokers, had singleton pregnancies, had no current occupational exposure to known developmental toxicants, and had no history of illicit drug use, no pregnancy-related diabetes, or hypertension were recruited.	Dietary consumption of PAH-rich food (meat and fish products that were grilled, roasted, or smoked) was assessed using an FFQ. Information was collected on usual dietary intake over a 1-y period prior to the interview. FFQ was validated within an adult population for nutrient and food groups. Assessed during the first trimester Treated as a continuous variable using food scores Dietary consumption of PAH-rich foods (fried, broiled, and barbecued meat) was assessed using a questionnaire. Authors mentioned validating the dietary questionnaire, but with no mention of the population in which it was validated. Assessed during the third trimester Treated as covariate (categorical variable) in the association between maternal urinary metabolites of naphthalene, 2-hydroxynaphthalene (2-OH NAP), and birth outcomes assessed	Birth weight, birth length, and head circumference Data obtained from medical records. Gestational age was estimated using LMP and the date of birth. Birth weight, birth length and head circumference Data obtained from medical records. Gestational age was estimated using LMP method and ultrasound data	Airborne PAHs, child's sex, gestational age, parity, maternal prepregnancy weight, weight gain in pregnancy, and prenatal environmental tobacco smoke
Lamichhane et al. ²⁶	Prospective cohort study Republic of Korea 2006–2011	A total of 1,825 nonsmoking pregnant people who had singleton pregnancies and were free from chronic diseases were recruited; 1,047 excluded from the final analysis due to multiple births, having diabetes or hypertension, and missing data on various exposures and outcomes [birth length, head circumference, birth weight, meat consumption, smoking, or urinary 2-naphthol (2-NAPH) and 1-OHP].	Dietary consumption of PAH-rich food (meat and fish products that were grilled, roasted, or smoked) was assessed using an FFQ. Information was collected on usual dietary intake over a 1-y period prior to the interview. FFQ was validated within an adult population for nutrient and food groups. Assessed during the first trimester Treated as a continuous variable using food scores Dietary consumption of PAH-rich foods (fried, broiled, and barbecued meat) was assessed using a questionnaire. Authors mentioned validating the dietary questionnaire, but with no mention of the population in which it was validated. Assessed during the third trimester Treated as covariate (categorical variable) in the association between maternal urinary metabolites of naphthalene, 2-hydroxynaphthalene (2-OH NAP), and birth outcomes assessed	Birth weight, birth length and head circumference Data obtained from medical records. Gestational age was estimated using LMP method and ultrasound data	Sex of the infant, parity, anthropometry of mother, gestational age, and intakes of vegetables, fruits, iron, and fish
Nie et al. ^{27a}	Prospective cohort study Taiyuan, China 2006–2011	A total of 287 pregnant women ≥ 18 y of age who had resided in Taiyuan for at least 1 y and were nonsmokers and had a single gestational viable fetus; 24 women were excluded due to chronic conditions and nonavailability of biological sample.	Dietary consumption of PAH-rich food (meat and fish products that were grilled, roasted, or smoked) was assessed using an FFQ. Information was collected on usual dietary intake over a 1-y period prior to the interview. FFQ was validated within an adult population for nutrient and food groups. Assessed during the first trimester Treated as a continuous variable using food scores Dietary consumption of PAH-rich foods (fried, broiled, and barbecued meat) was assessed using a questionnaire. Authors mentioned validating the dietary questionnaire, but with no mention of the population in which it was validated. Assessed during the third trimester Treated as covariate (categorical variable) in the association between maternal urinary metabolites of naphthalene, 2-hydroxynaphthalene (2-OH NAP), and birth outcomes assessed	Birth weight, birth length, head circumference, ponderal index, and cephalization index Data obtained from medical records. Gestational age was estimated using LMP method and ultrasound data	Parity, maternal BMI, maternal age, gender of newborn, gestational age, eating grilled meat, passive smoking, and levels of the other three PAH metabolites, urinary phenol, and cord blood lead

Table 1. (Continued.)

Author details	Study design, location and period	Population, sampling procedure, and follow-up	Exposure assessment	Outcome measurement	Covariates
Perera et al. ^{28a}	Prospective cohort study Washington Heights, Central Harlem, and South Bronx, New York, USA 01/1998 and 06/2005	A total of 298 mothers who were 18–35 y of age, nonsmokers, registered at the obstetrics and gynecology clinics by the 20th week of pregnancy, and free of diabetes, hypertension, or HIV; and had resided in the area for at least 1 y were recruited. A total of 84 mothers were excluded from the final analysis due to missing data.	Dietary consumption of PAH-rich foods (frequency of eating fried, broiled, or barbecued food during the last 2 wk of the third trimester of pregnancy) was assessed using a questionnaire. Assessed during the last (third) trimester. Treated as a covariate (categorical variable) in the associations between environmental exposures (BaP-DNA exposure, environmental tobacco smoke, cotinine) and birth outcomes.	Birth weight, birth length, and head circumference Data obtained from medical records. Gestational age estimated based on LMP	Ethnicity, sex of newborns, maternal BMI, dietary PAH consumption, and gestational age
Wu et al. ²⁹	Prevalence Case–Control Study Tianjin, China April and November 2007	A total of 81 women who experienced missed abortion (occurred before 14 wk of gestation) were matched with women with normal pregnancies but requested an induced abortion due to an unplanned and unwanted pregnancy. Matching was based on the hospital, maternal age, and gravidity. Smokers, women with chronic diseases and pregnancy complications, women with potentially high occupational exposures to PAH, and those who had resided in the study area (Tianjin) for less than a year, were excluded.	Dietary consumption of PAH-rich foods (smoked, grilled, barbecued foods 1–2 times/wk) was assessed using a questionnaire. Assessed after abortion procedure Treated as a dichotomous variable	Missed abortion Ultrasound measurement was used to confirm abortion occurred before 14 wk of gestation.	Maternal education and household income

Note: B(a)P, benzo(a)pyrene; BMI, body mass index; FFQ, Food Frequency Questionnaire; HIV, human immunodeficiency virus; LMP, last menstrual period; LOD, limit of detection; PAH, polycyclic aromatic hydrocarbons.

^aThe relationship was assessed indirectly through an evaluation of the potential confounding role of dietary PAH exposure in their multivariable analysis.

demographic or birth anthropometrics data and inconsistencies in the birth anthropometrics data. However, it is unclear whether the study by Jedrychowski et al.²⁵ actually excluded participants with missing data (i.e., unavailability of biological sample) from the analysis. Three studies^{26,28,29} reported that excluded participants were not significantly different from the participants retained in the study. Two of the studies (Nie et al.²⁷ and Wu et al.²⁹) had relatively small sample sizes, which raised concerns about generalizability of the study findings. The five cohort studies^{24–28} did not provide any information on losses to follow-up. Using the risk of bias assessment tool, selection bias was considered low in the Duarte-Salles et al.²⁴ study, moderate in four studies,^{25–28} and high in the Wu et al.²⁹ study (Table 2).

Information bias was a validity concern in some of the included studies. Even though all the included studies reported collecting the dietary data using a questionnaire, only two studies^{24,26} mentioned the type of dietary assessment tool used i.e., FFQ. Of the two studies, only the Duarte-Salles et al.²⁴ study provided details on the quantification process of dietary PAH exposure. Lamichhane et al.,²⁶ however, generated PAH food score based on the frequency of consumption of PAH-rich foods. Use of questionnaires in assessing dietary exposure is, however, subject to recall bias. The FFQ used by the two studies were validated but were done with respect to nutrients and food groups and not dietary PAH. The Nie et al.²⁷ study reported validating the dietary questionnaire but provided no information on the population in which the tool was validated and the validation process.

For the prevalence case–control study (Wu et al.²⁹) there was no mention in the report as to whether the field personnel were blinded to the case–control status of the participants. Only one (Jedrychowski et al.²⁵) of the prospective cohort studies assessed dietary PAH exposure at different time points throughout the pregnancy i.e., first, second, and third trimesters. The other cohort studies^{24,26–28} assessed PAH exposure at one time point. The assessment was conducted in the first trimester in the Lamichhane et al.²⁶ study, second trimester in the Duarte-Salles et al.²⁴ study, and third trimester in the studies conducted by Nie et al.²⁷ and Perera et al.²⁸ All the studies reported that information on the outcomes were obtained from medical records. Outcome misclassification was therefore minimized in all the included studies. Two studies (Jedrychowski et al.²⁵ and Perera et al.²⁸) used the LMP method only to estimate gestational age. Abortion was confirmed by ultrasound method in the prevalence case–control study (Wu et al.²⁹). The Nie et al. study²⁷ did not mention the method used for estimating gestational age. Assessing validity of the outcome measures in this study was therefore impossible. Using the risk of the bias assessment tool, risk of information bias was considered low in the Duarte-Salles et al.²⁴ study, moderate in the Lamichhane et al.²⁶ study, and high in the four remaining studies^{25,27–29} (Table 2).

All the included studies adjusted for potential confounders in the multivariable analysis. Using the risk of the bias assessment tool, risk of confounding bias was considered low in three of the studies,^{24–26} moderate in the Wu et al.²⁹ study, and high in two studies^{27,28} (Table 2). The two studies (Nie et al.²⁷ and Perera et al.²⁸) were rated as having high confounding bias because they assessed the dietary PAH–birth outcome relationship indirectly by conducting separate analyses (sensitivity analyses) that included dietary PAH exposure and other covariates that were initially adjusted in the main model. The two studies were therefore considered as not controlling for any potential confounders in the analysis.

Based on the NIH Study Quality Assessment Tool, three studies each were rated as fair^{25,27–29} and good^{24,26} quality (Tables 3

Table 2. Risk of bias in included studies.

	Selection bias			Information bias			Confounding bias		
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Duarte-Salles et al. ²⁴	X	—	—	X	—	—	X	—	—
Jedrychowski et al. ²⁵	—	X	—	—	—	X	X	—	—
Lamichhane et al. ²⁶	—	X	—	—	X	—	X	—	—
Nie et al. ²⁷	—	X	—	—	—	X	—	—	X
Perera et al. ²⁸	—	X	—	—	—	X	—	—	X
Wu et al. ²⁹	—	—	X	—	—	X	—	X	—

Note: Evaluation undertaken using Dekkers et al.²² recommendations. For selection bias, sample representativeness, participation and response rate, missing data, attrition rate (for prospective studies), and data restrictions during the analysis were evaluated. For information bias, the exposure and outcome assessment methods were evaluated. For confounding bias, evidence of the studies' controlling of potential confounders of the relationship in the multivariable analysis was searched. —, no data.

and 4). The studies rated as good quality clearly stated the research questions/objectives, clearly defined the study population, selected both exposed and unexposed population from the same study base, ensured that exposure measurement preceded outcome ascertainment, ensured that the study period was long enough for the association between exposure and outcome to be established, investigated exposure–response relationship, measured both exposure and outcome consistently across all study participants, assessed exposure at more than one time point, and ensured that confounding control was adequate. For studies rated as fair quality; the study period was not long enough for accurate determination of the association between exposure and outcome, exposure–response relationship was not investigated, exposure was assessed at one time point, and extent of losses to follow-up could not be established.

Summary Effect Estimates and Evidence of Statistical Heterogeneity

In the main analysis, dietary PAH consumption was associated with a lower birth weight (5.65 g; 95% CI: –16.36, 5.06) and shorter birth length (0.04 cm; 95% CI: –0.08, 0.01) (Table 5; Figure 2). A high level of heterogeneity was noted among the five studies meta-analyzed for these outcomes (Birth weight: $I^2 = 86.48\%$, $p = 0.0001$; Birth length: $I^2 = 65.13\%$, $p = 0.0091$). Again in the main analysis, dietary PAH exposure was associated with 0.001 cm (95% CI: –0.003, 0.005) greater head circumference, with no heterogeneity observed in the two studies that provided estimates for this outcome ($I^2 = 0.00\%$; $p = 0.30$). The 95% CIs of all three estimates, however, included the null value.

In sensitivity analysis (Table 6) restricting the analysis to studies that examined dietary PAH as the main exposure,^{24–26} dietary PAH exposure was associated with 14.61 g (95% CI: –21.07, –8.15), 0.06 cm (95% CI: –0.1, –0.03) and 0.13 cm (95% CI: –0.46, 0.19) lower birth weight, shorter birth length, and smaller head circumference, respectively. The effect size for the dietary PAH–head circumference relationship included the null value. Low levels of heterogeneity were observed among the birth weight and birth length studies meta-analyzed (Birth weight: $I^2 = 0.00\%$, $p = 0.7176$; Birth length: $I^2 = 0.02\%$, $p = 0.2399$). A high level of heterogeneity was observed among the head circumference studies meta-analyzed ($I^2 = 68.76\%$; $p = 0.0736$).

Evidence of Publication Bias

The trim-filled funnel plots for all the outcomes with the exception of birth weight were asymmetrical and suggestive of evidence of publication bias (Figures 3 and 4). However, the Begg's and Egger's tests did not confirm the funnel plot asymmetry observed in the funnel plots. The adjusted estimates after accounting for publication bias remained largely similar to the unadjusted estimates except for the birth length, which was marginally greater (Table 7).

Discussion

Summary of Findings

Dietary PAH consumption was associated with lower birth weight (5.65 g; 95% CI: –16.36, 5.06) and shorter birth length (0.04 cm; 95% CI: –0.08, 0.01), and greater head circumference (0.001 cm; 95% CI: –0.003, 0.005). The 95% CI of all the summary effect estimates, however, included the null value.

Validity Issues

An exhaustive literature search of the PubMed and Scopus databases, which index the bulk of scientific journals, was performed and enabled identification of relevant articles for inclusion in the study. We also screened the reference lists of all the included studies and previous related reviews on the topic to ensure that we did not miss any relevant articles. The review was focused on studies of any epidemiological design and published in any language owing to the limited evidence on the topic.

The methodological quality of the included studies was thoroughly evaluated using both quantitative and qualitative tools. Sensitivity analyses were conducted by restricting the analysis to studies that explored PAH as the main exposure to assess robustness of the study findings. These studies were prospective cohort studies and were rated as good on the NIH Grading Assessment for Prospective Studies. We could not undertake a dose–response analysis and were also unable to establish the critical window of susceptibility during pregnancy owing to limited data and assessment of exposures at different time points among the studies reviewed.

Funnel plot and Begg's and Egger's tests were used to explore publication bias to help account for unpublished studies. The Cochran χ^2 test was used to quantify the level of heterogeneity in the meta-analyses.

Synthesis with Previous Evidence

Dietary PAH was found to be associated with lower birth weight, shorter birth length, and greater head circumference. Based on a systematic literature search, our systematic review and meta-analysis is, to our knowledge, the first to summarize the evidence on dietary PAH exposure and adverse birth outcomes. Our findings are consistent with the findings of a review conducted by Yang et al.¹⁷ The Yang et al.¹⁷ review was the first to examine the effect of prenatal airborne PAH exposure and found no significant association between prenatal airborne PAH exposure (OR = 0.97; 95% CI: 0.93, 1.01), PAH-DNA adducts in cord blood (OR = 1.0; 95% CI: 0.97, 1.03) and 1-HP in maternal urine (OR = 1.0; 95% CI: 0.97, 1.03), and birth weight. The authors reported that the null relationship observed could be attributed to the lack of high-quality epidemiological studies and wide heterogeneities observed in the included studies. Similarly, in this review, there was considerable heterogeneity in the measurement of dietary PAH exposure

Table 3. NIH grading assessment for prospective studies.

Criteria	Duarte-Salles et al. ²⁴				Jedrychowski et al. ²⁵				Lamichhane et al. ²⁶				Nie et al. ²⁷				Perara et al. ²⁸			
	Yes	No	CD, NR, NA		Yes	No	CD, NR, NA		Yes	No	CD, NR, NA		Yes	No	CD, NR, NA		Yes	No	CD, NR, NA	
1. Was the research question or objective in this paper clearly stated?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
2. Was the study population clearly specified and defined?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
3. Was the participation rate of eligible persons at least 50%?	—	X	—		—	—	X		—	—	X		—	—	X		—	—	X	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
5. Was a sample size justification, power description, or variance and effect estimates provided?	—	—	X		—	—	X		—	—	X		—	—	X		—	—	X	
6. For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome(s) being measured?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	X	—	—		—	—	—		X	—	—		—	X	—		—	X	—	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	X	—	—		—	X	—		X	—	—		X	—	—		—	X	—	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
10. Was the exposure(s) assessed more than once over time?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
12. Were the outcome assessors blinded to the exposure status of participants?	—	—	X		—	—	X		—	—	X		—	—	X		—	—	X	
13. Was loss to follow-up after baseline 20% or less?	X	—	—		—	—	X		—	—	X		—	—	X		—	—	X	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	X	—	—		X	—	—		X	—	—		X	—	—		X	—	—	
Overall rating	Good				Good				Good				Fair				Fair			

Note: Grading undertaken using NIH Study Quality Assessment Tool (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>).²¹ —, no data; CD, cannot determine; NA, not applicable; NR, not reported; NIH, National Institutes of Health.

Table 4. NIH grading assessment for case-control study.

Criteria	Wu et al. ²⁹		
	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this paper clearly stated and appropriate?	X	—	—
2. Was the study population clearly specified and defined?	X	—	—
3. Did the authors include a sample size justification?	—	—	X
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	X	—	—
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	X	—	—
6. Were the cases clearly defined and differentiated from controls?	X	—	—
7. If <100% of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	—	—	X
8. Was there use of concurrent controls?	—	X	—
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	—	—	X
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	X	—	—
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	X	—	X
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	X	—	—
Overall rating	Fair		

Note: Grading undertaken using NIH Study Quality Assessment Tool (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>).²¹ —, no data; CD, cannot determine; NA, not applicable; NR, not reported; NIH, National Institutes of Health.

among the included studies. The majority of the included studies also used nonstandardized and validated dietary questionnaires for assessing PAH exposure with potential exposure misclassification. These issues are likely to impact the summary effect estimates computed. However, we expect any exposure measurement error to be random (not associated with the outcome measurement), resulting in nondifferential misclassification and biasing the effect estimate toward the null.

The results from the sensitivity analysis confirms the impact of the considerable heterogeneity among the included studies and potential exposure misclassification on the summary effect estimates computed. For the birth weight sensitivity analysis, the two included studies (Duarte-Salles et al.²⁴ and Lamichhane et al.²⁶) used a validated FFQ in the assessment of PAH exposure. There was less heterogeneity in the exposure assessment method across the two studies. In addition, validated FFQ are very robust, especially the semiquantitative FFQ used in the Duarte-Salles et al.²⁴ study, and minimizes exposure misclassification. In the birth length sensitivity analysis, the Jedrychowski et al.²⁵ study was the third study and used a detailed dietary questionnaire in the assessment of PAH exposure. The exposure assessment method applied in this study is comparable to the FFQ used in the studies by Duarte-Salles et al.²⁴ and Lamichhane et al.²⁶; however, the

tool was not validated. The sensitivity analysis also addressed the issue of unmeasured confounding because it considered only studies for which dietary PAH was the main exposure of interest. Unmeasured confounding was a problem in the studies conducted by Nie et al.²⁷ and Perera et al.²⁸ which examined dietary PAH as a confounder. It is worth noting that the Duarte-Salles et al.²⁴ study contributed the largest weight to the summary effect sizes computed for birth weight and birth length. Even though other studies contributed to the summary effect size computed, this Norwegian study, which was highly powered and had the highest methodological quality, most probably better elucidates the relationship between dietary PAH exposure and adverse birth outcomes in Western populations and similar populations with low levels of ambient PAH exposure.

It is worth mentioning that we observed high heterogeneity in the birth weight analysis in comparison with the birth length analysis. This finding could be as a result of the considerable variability in the effect estimates reported by the included studies, which obviously impacts the study weights. Nie et al.²⁷ for instance reported a positive association with a very wide CI ($\beta = 8.69$; 95% CI: $-7.23, 24.61$), whereas Perera et al.²⁸ reported a very small negative association with a very narrow CI ($\beta = -0.01$; 95% CI: $-0.01, -0.00$). The other two studies (Duarte-Salles

Table 5. Summary effect size (ES) for the relation of dietary PAH exposure with birth outcomes.

Outcomes	Studies included	Random effects model		Heterogeneity		
		ES	95% CI	Cochran χ^2	p-Value	I ² (%)
Birth weight ^a	<i>n</i> = 4: Duarte-Salles et al., ²⁴ Lamichhane et al., ²⁶ Nie et al., ²⁷ Perera et al., ²⁸	−5.65	−16.36, 5.06	20.9	0.0001	86.48
Birth length	<i>n</i> = 5: Duarte-Salles et al., ²⁴ Lamichhane et al., ²⁶ Jedrychowski et al., ²⁵ Nie et al., ²⁷ Perera et al. ²⁸	−0.04	−0.08, 0.01	13.5	0.0091	65.13
Head circumference	<i>n</i> = 4: Lamichhane et al., ²⁶ Jedrychowski et al., ²⁵ Nie et al., ²⁷ Perera et al. ²⁸	0.001	−0.003, 0.005	3.56	0.3129	0.000

^aJedrychowski et al.²⁵ was excluded because the study did not provide independent estimates for dietary PAH exposure. —, no data; CI, confidence interval; ES, effect size; PAH, polycyclic aromatic hydrocarbons.

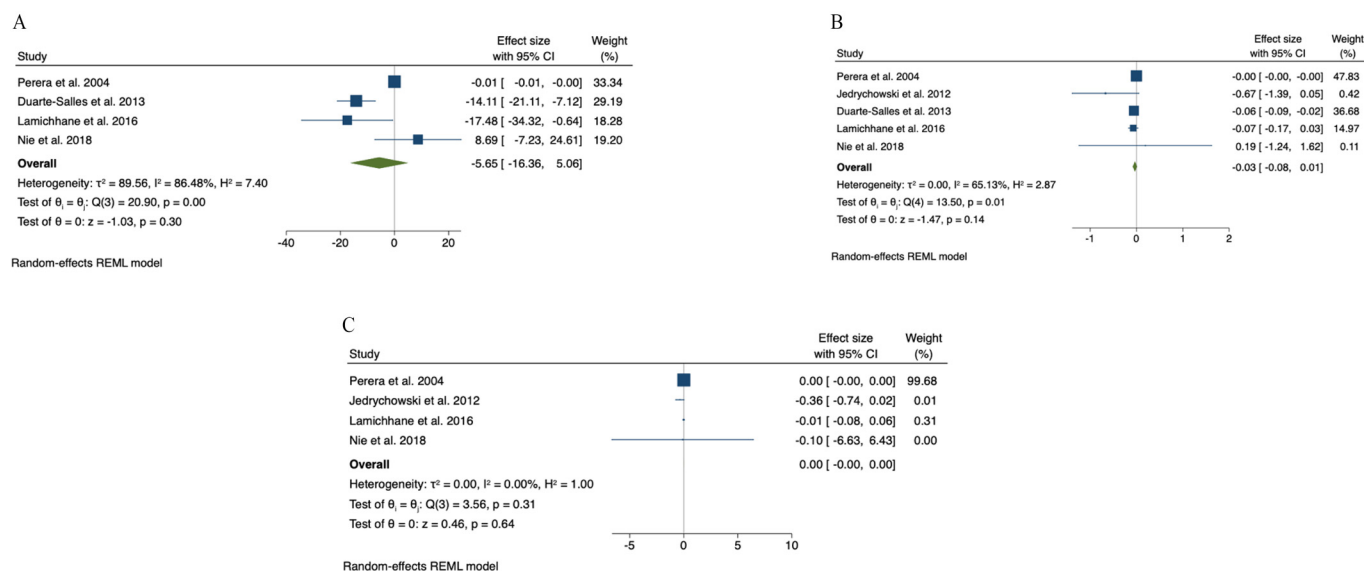


Figure 2. Forest plot showing the association of dietary PAH exposure with birth anthropometric measures. Birth weight (A), birth length (B), and head circumference (C). Note: CI, confidence interval; PAH, polycyclic aromatic hydrocarbons.

et al.²⁴ and Lamichhane et al.²⁶) reported negative associations of similar magnitude and wider CIs ($\beta = -14.12$; 95% CI: $-21.11, -7.12$ and $\beta = -17.48$; 95% CI: $-34.32, -0.64$, respectively). The situation was different with the birth length analysis, where the effect estimates of the five studies meta-analyzed were generally similar in magnitude and size of CIs. All the included studies with the exception of the Nie et al.²⁷ study reported small negative associations. The Nie et al.²⁷ study had the smallest weight in the meta-analysis together with the Jedrychowski et al.²⁵ study, which reported the largest negative association and the widest CI of the four studies that reported negative associations.

Maternal active and passive smoking, which exposes mothers to PAHs, has also been associated with the risk of adverse birth outcomes.^{30,31} In a meta-analysis involving 124 studies, Quelhas et al.³⁰ reported that in comparison with nonsmokers, mothers' active tobacco use during pregnancy was associated with higher odds of SGA (OR = 1.95; 95% CI: 1.76, 2.16), shorter birth length [mean difference (MD) = 0.43; 95% CI: 0.41, 0.44], and smaller head circumference (MD = 0.27; 95% CI: 0.25, 0.29) at birth. Similarly, in a review by Di et al.,³¹ maternal smoking during pregnancy was significantly associated with the risk of low birth weight (OR = 1.89; 95% CI = 1.80, 1.98). Both reviews observed a dose-response relationship for all outcomes examined. In addition, the reviews observed high statistical heterogeneity in the meta-analysis.

A number of prospective cohort studies have also found PAH exposure^{32–37} and acrylamide,^{38,39} a carcinogenic pollutant that is abundant in dietary sources, to be associated with increased risk of adverse birth outcomes. Acrylamide has been reported to have anthropogenic sources similar to those of PAH because it is also generated by cooking practices, such as roasting.^{40,41} Acrylamide exposure is therefore likely to be a potential confounder of the

dietary PAH–birth outcomes relationship and could be an alternative explanation of the observed relationship. Choi et al.³² reported that prenatal airborne PAH exposure was significantly associated with reductions in birth weight, birth length, and head circumference among Krakow Caucasians and New York City African Americans. Choi et al.³³ found PAH exposure from both dietary and airborne sources in the first trimester to be associated with the largest decrease in fetal growth ratio (-3% ; 95% CI: $-5\%, -0\%$), birth weight (-105 g; 95% CI: $-188, -22$ g), and birth length (-0.78 cm; 95% CI: $-1.30, -0.26$ cm) in comparison with exposure in other trimesters. The study also reported an increasing trend in the case cephalization index (head-to-weight ratio) and to some extent substantiates our findings on head circumference because head circumference is a predictor of cephalization index. Polanska et al.³⁴ found the combined effect of PAH (OH-PHE) and tobacco (cotinine) markers to be significantly associated with the cephalization index, which also to some extent substantiates our findings on head circumference. Polanska et al.,³⁴ however, found no significant association between the individual PAH exposure markers and all the birth outcomes studied.

As was observed in the present study, Yang et al.³⁷ also found PAH markers [prenatal urinary 2-hydroxynaphthalene (2-OHNA), P OHNA (sum of 1- and 2-OHNA), and sum of monohydroxy-PAH (P OH-PAHs)] to be associated with shorter birth length. Freije et al.³⁵ also observed an inverse association between 2-OH-NAP, a PAH marker, and gestational age. In both studies,^{35,37} maternal urine samples were used, implying that the exposure measurement reflects both ambient and dietary PAH exposure. Jedrychowski et al.³⁶ found prenatal exposure to airborne PAH to be negatively associated with height gain among newborns.

Table 6. Sensitivity analysis restricting the analysis to studies with dietary PAH consumption as the main exposure.

Outcomes	Studies included	Random effects model		Heterogeneity		
		ES	95% CI	Cochran χ^2	p-Value	I^2 (%)
Birth weight	$n = 2$: Duarte-Salles et al., ²⁴ Lamichhane et al. ²⁶	-14.61	-21.07, -8.15	0.13	0.7176	0.00
Birth length	$n = 3$: Duarte-Salles et al., ²⁴ Lamichhane et al., ²⁶ Jedrychowski et al. ²⁵	-0.06	-0.1, -0.03	2.82	0.2399	0.02
Head circumference	$n = 2$: Lamichhane et al., ²⁶ Jedrychowski et al. ²⁵	-0.13	-0.46, 0.19	3.15	0.0758	68.27

Note: —, no data; CI, confidence interval; ES, effect size; PAH, polycyclic aromatic hydrocarbons.

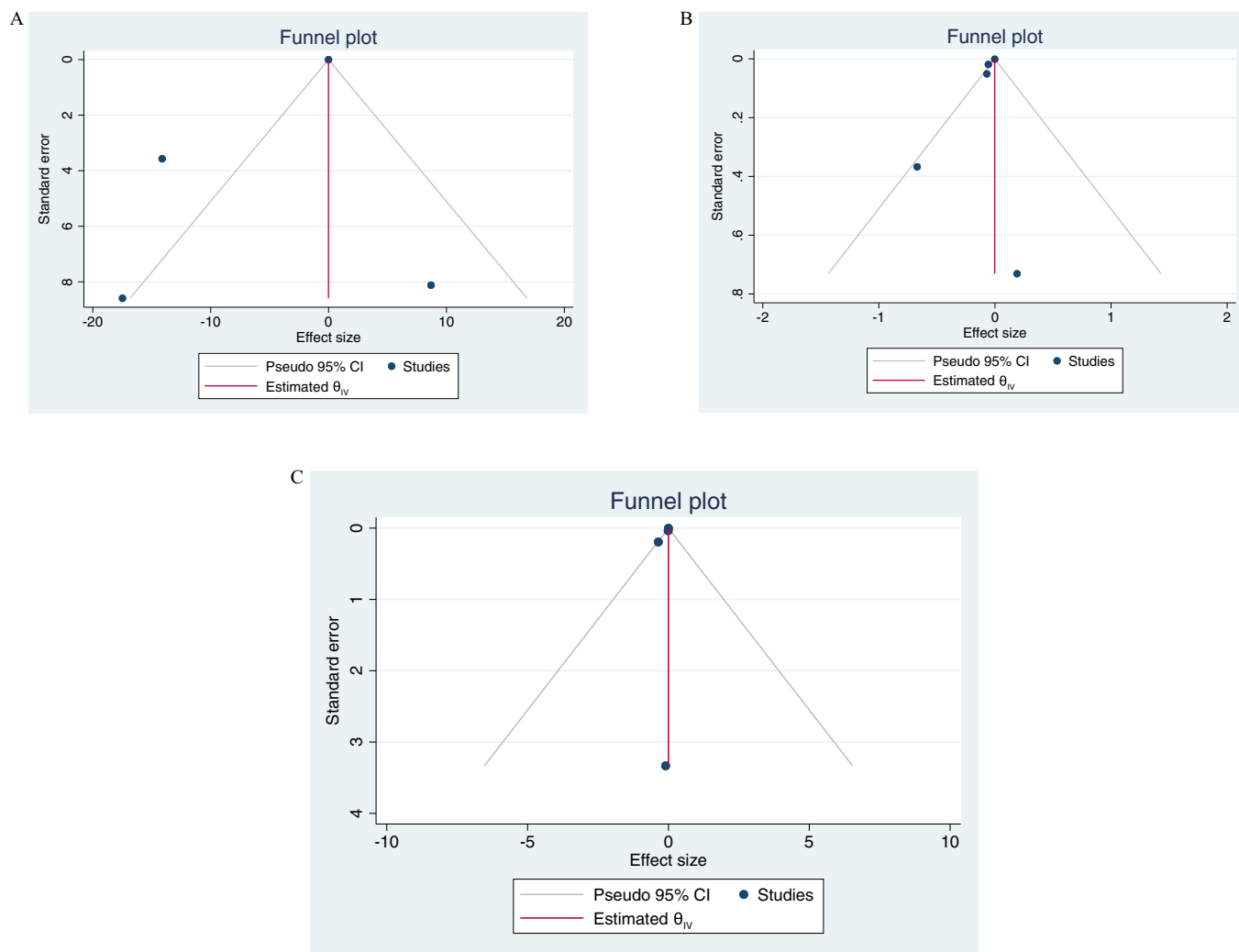


Figure 3. Funnel plot for the association of dietary PAH exposure with birth anthropometric measures: birth weight (A), birth length (B), and head circumference (C). Note: CI, confidence interval; PAH, polycyclic aromatic hydrocarbons.

Comparing the findings of this review on dietary PAH exposure to those of the Yang et al.¹⁷ review that examined airborne PAH exposure and the primary studies on PAH exposure (Choi et al.^{32,33}) is important for elucidating the overall effect of PAH as a reproductive toxicant and also provides an opportunity to establish the most important route of exposure as it relates to reproductive toxicity. The Yang et al.¹⁷ review focused on narrowly defined exposure metrics that likely included both diet and airborne exposures in the case of the biomarker-specific analysis (PAH DNA adducts and 1-HP concentration) they performed. Our review, however, focused primarily on dietary exposure metrics. Although the earlier Choi et al.³² study focused on airborne PAH, their later study³³ focused on both dietary and airborne PAH. Yang et al.¹⁷ also found the overall summary effect size for airborne PAHs and PAH-DNA adducts to be impacted by high levels of heterogeneity and attributed it to possible lack of coherence in exposure quantification as it relates to PAH measurements. Evaluation of the whole body of evidence including ours seems to suggest that dietary exposure is an important route of exposure when assessing the toxicity of PAH on reproductive health and calls for the conduct of more studies to solidify the evidence base.

Biological Plausibility

The lipophilic nature of PAHs facilitates their absorption by binding to the cell membrane.^{4,15,42} Benzo[a]pyrene (BaP), which has been

noted to be the easiest to dissolve in lipids, is the most studied as it relates to health effect assessment.¹⁵ By binding to lipid transporters, such as chylomicrons and other lipoproteins, BaP has been observed to be easily absorbed and distributed in various organs and promoting its bioaccumulation as a result.⁴²

During pregnancy, PAHs have been reported to easily cross the placenta by binding to aromatic hydrocarbon receptor (AhR) on the placenta, thereby posing a significant threat to the developing fetus.^{15,43} In an animal model study by Detmar et al.,⁴⁴ chronic PAH exposure was reported to cause abnormalities in the placental vasculature, resulting in reductions in surface area and volume of the fetal arterial vasculature of the placenta. This process can consequently lead to inhibition of fetal access to critical growth factors, such as blood, oxygen, and glucose,¹⁵ thereby resulting in poor fetal development. Deficiency in such critical nutrients may contribute to poor fetal growth and birth anthropometrics as reported in this study. Similarly, in a mouse model by Sanyal and Li,⁴⁵ maternal exposure to PAHs such as BaP and 7,12-dimethylbenz[α]anthracene was found to result in significant fetal growth retardation as well as necrosis of placental tissues. For both toxicants, the high level of toxicity resulted in damage to fetal blood vessels in multiple organs, a situation that poses a significant threat to fetal development.

Fetal exposure to PAHs in the first trimester has also been noted to impair the organ development process.²⁵ Zhan et al.⁴⁶ in

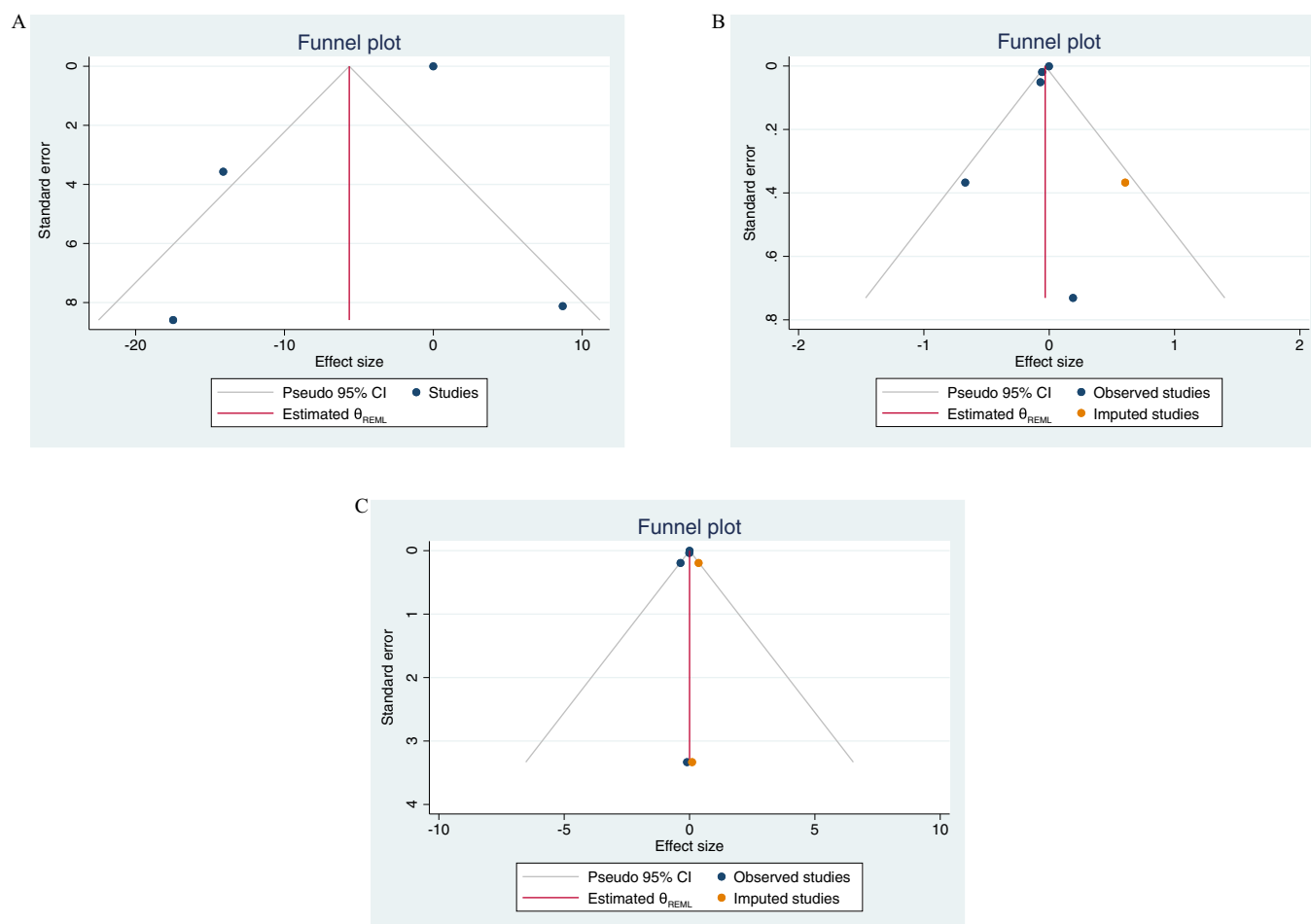


Figure 4. Filled Funnel plot for the association of dietary PAH exposure with birth anthropometric measures. Birth weight (A), birth length (B), and head circumference (C). Note: CI, confidence interval; PAH, polycyclic aromatic hydrocarbons.

an experimental model using mice showed that BaP could seriously disrupt cell growth and genomic DNA stability, as well as increase cell apoptosis thereby affecting fetal health. Cao et al.⁴⁷ noted that prenatal PAH exposure may contribute to an increased risk of low birth weight—inducing epigenetic changes such as the modulation of DNA methylation states of genomic DNA and growth-related genes in umbilical cord blood. In an animal model by Laknaur et al.⁴⁸ BaP exposure during gestation was attributed to epigenetic changes that facilitate the expression of contractile-associated factors through the NF κ B pathway that consequently increase the occurrence of preterm birth.

Furthermore, PAH metabolism has been reported to lead to the generation of metabolites such as diol-epoxides and radical cations, which may lead to the formation of DNA adducts.⁴² These DNA adducts have been reported to underlie biochemical disruptions and cellular damage, consequently causing carcinogenic, mutagenic, immunosuppressive, and teratogenic damage.⁴² As has been shown by Perera et al.,⁴⁹ PAH-DNA adducts are significantly

associated with birth weight, birth length, and head circumference. Maternal BaP exposure in rats has also been reported to cause a dose-dependent decrease in fetal survival (25 $\mu\text{g}/\text{m}^3$, 78.3% per litter; 75 $\mu\text{g}/\text{m}^3$, 38.0% per litter; 100 $\mu\text{g}/\text{m}^3$, 33.8% per litter; $p < 0.05$) in rat litters.⁵⁰ This evidence does seem to support the adverse effects of PAH in missed abortion as reported by the Wu et al.²⁹ study.

Conclusion

This systematic review and meta-analysis provide evidence of a potential association between dietary PAH exposure and adverse birth outcomes. We found lower birth weight and shorter birth length to be associated with dietary exposure to PAH. The strength of the summary effect estimates is, however, likely to be impacted by the considerable heterogeneity in the measurement of exposure among the included studies and the nonstandardized and validated dietary questionnaires employed by majority of the

Table 7. Test for publication bias and adjusted summary effect size/estimate.

Outcome	Begg's test		Egger's test			Adjusted summary estimate		
	z-Score	p-Value	Bias coefficient	SE	p-Value	No. of studies	ES	95% CI
Birth weight	-1.02	0.7341	-0.35	1.942	0.8581	4	-5.65	-16.36, 5.06
Birth length	-0.24	1.0	-1.04	0.604	0.0855	6	-0.03	-0.08, 0.01
Head circumference	-1.02	0.7341	-0.75	0.591	0.2016	6	0.001	-0.003, 0.005

Note: CI, confidence interval; ES, effect size; SE, standard error.

included studies. This likelihood underscores the need for high-quality epidemiological studies that are prospective in design, use improved exposure assessment methods to allow for the conduct of dose–response analysis, and establish the critical window of susceptibility to PAH exposure. The evidence from our study suggests counseling of pregnant women during antenatal visits to avoid consumption of grilled, smoked, and roasted foods, which are high in PAH and can have adverse consequences for the developing fetus.

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